UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

IN RE: TESTOSTERONE REPLACEMENT THERAPY PRODUCTS LIABILITY LITIGATION	MDL No. 2545
This Document Relates to All Cases	Master Docket Case No. 1:14-cv-01748 Hon. Judge Matthew F. Kennelly

APPENDIX A
(Studies Showing Low-T is a Cardiovascular Risk)[1]

	Study	Key Finding
1	Gerald B. Phillips et al., *The Association of Hypotestosteronemia With Coronary Artery Disease in Men*, 14 ARTERIOSCLER. THROMB. VASC. BIOL. 701 (1994).	"Testosterone correlated negatively with CAD [coronary artery disease] in each of the four groups."
2	K.M. English, *Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms*, 21 EURO. HEART J. 890 (2000)	"Men with proven coronary heart disease had significantly lower levels of both free and bioavailable testosterone, and free androgen index than normal controls . . . . Total cholesterol level was significantly lower in cases than in controls . . . ."
3	Kay-Tee Khaw et al., *Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study*, 116 CIRCULATION 2694 (2007)	"Mean testosterone concentrations were lower in men who died of any cause, cardiovascular disease, or cancer than in control subjects."
4	Gail A. Laughlin et al., *Low Serum Testosterone and Mortality in Older Men*, 93 J. CLIN. ENDOCRINOL. METAB. 68 (2008)	"In age-, adiposity-, and lifestyle-adjusted analyses of cause specific mortality, low total and bioavailable testosterone were each significantly associated with elevated 20-yr risk of CVD [cardiovascular disease] mortality and death due to respiratory disease . . ." Researchers further found, "The risk estimates for total testosterone were stronger for cardiovascular .

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[1] Copies of these studies are maintained in Defendants' files, and they will gladly provide them to chambers should the Court like to review any or all of them.

		. . death when deaths that occurred during the first 5 yr of follow-up were excluded, suggesting that the testosterone-mortality association is not explained by concurrent disease, whether known or hidden."
5	Robin Haring et al., *Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79*, 31 EURO. HEART J. 1494 (2010)	"We showed that in a sample of men aged 20-79 men with serum testosterone levels below 8.7 nmol/L (250 ng/dL) had more than two-fold increased risk of mortality from all causes compared with those with higher serum testosterone levels, independent of age, WC [waist circumference], smoking habits, high-risk alcohol use, and physical activity."
6	Giovanni Corona et al., *Low Testosterone is Associated with an Increased Risk of MACE Lethality in Subjects with Erectile Dysfunction*, 7 J. SEX. MED. 1557 (2010)	"[W]e found an association between incident CV death and hypogonadism-related symptom and signs . . . even after adjustment for confounding factors."
7	S.R. Pye et al., *Late-Onset Hypogonadism & Mortality in Aging Men*, 99 J. CLIN. ENDOCRINOL. METAB. 1357 (2014)	"Compared with men with LOH [late on-set hypogonadism], those with moderate and severe LOH had a 3-fold . . . and 8-fold . . . higher risk of CVD [cardiovascular disease] mortality, respectively, after adjustment for cofounders."
8	Asa Tivesten et al., *Low Serum Testosterone and Estradiol Predict Mortality in Elderly Men*, 94 J. CLIN. ENDOCRINOL. METAB. 2482 (2009)	"Our results show that risk of death increased for elderly men in the lowest quartile of both testosterone and estradiol levels. Testosterone and estradiol predicted death independently of each other, and risk of death nearly doubled (96% increase) in subjects with both low testosterone and low estradiol compared with subjects within quartiles 2-4 of both hormones."
9	Claes Ohlsson et al., *High Serum Testosterone is Associated with Reduced Risk of Cardiovascular Events in Elderly Men*, 58 J. AM. COLLEGE CARDIOLOGY 1674 (2011)	"Our findings of a significant inverse association between testosterone levels and risk of combined fatal and nonfatal CV [cardiovascular] events in men support and extend previous work showing an association between testosterone and CV mortality."
10	Vakkat Muraleedharan et al., *Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes,* 169 EURO. J. ENDOCRINOL. 725 (2013)	"Mean baseline testosterone levels were significantly low in patients who died . . . when compared with those who are alive . . . . The mortality rate was 17.2% (41/238) in the low testosterone group compared with 9% (31/343) in the normal testosterone group."
		Researchers further found, "[A] sub-analysis of men with TT [total testosterone] less than the normal range did detect an increased risk of CV mortality compared with those with levels within the normal range."

11	Bu B. Yeap et al., *In Older Men an Optimal Plasma Testosterone is Associated with Reduced All-Cause Mortality and Higher Dihydrotestosterone With Reduced Ischemic Heart Disease Mortality, While Estradiol Levels Do Not Predict Mortality*, 99 J. CLIN. ENDOCRINOL. METAB. E9 (2014)	"In older men, having total T levels in the middle two quartiles at baseline predicted reduced incidence of death from any cause, as did having calculated free T or DHT [dihydrotestosterone] levels in the third quartile."
12	Slawomir Dobrzycki et al., *An assessment of correlations between endogenous sex hormone levels and the extensiveness of coronary heart disease and the ejection fraction of the left ventricle in males*, 50 J. MED. INVESTIGATION 162 (2003)	"After adjustment for cofounders, endogenous sex hormone levels remained essentially lower in men with proven coronary heart disease. Moreover, free testosterone levels were negatively correlated with the extensiveness of atherosclerosis in the coronary bed." (Citation omitted).
13	Masahiro Akishita et al., *Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors*, 210 ATHEROSCLEROSIS 232 (2010)	"In this follow-up study of middle-aged Japanese men with coronary risk factors, a low plasma testosterone level was associated with CV [cardiovascular] events."
14	Xiaorong Hu et al., *Low testosterone level in middle-aged male patients with coronary artery disease*, 22 EURO. J. INTERNAL MED. e133 (2011)	"In the present study, we found that the testosterone levels in CAD [coronary heart disease] patients were significantly lower than that in the control group . . . ."
15	Chris J. Malkin et al., *Low serum testosterone and increased mortality in men with coronary heart disease*, 96 HEART 1821 (2010)	"The present data have confirmed that low endogenous bio-T is related to all-cause and vascular mortality in coronary disease population." Researchers further added, "We have demonstrated that testosterone deficiency is associated with premature death in a cohort of patients with vascular disease; many of these patients died and will continue to die from cardiovascular disease."
16	Judith S. Brand et al., *Testosterone, Sex Hormone-Binding Globulin and the Metabolic Syndrome in Men: An Individual Participant Data Meta-Analysis of Observational Studies*, 9 PLoS ONE 1 (2014)	"[M]en with low concentrations of TT [total testosterone] . . . and FT [free testosterone] were more likely to have MetS [metabolic syndrome] compared to those having high sex hormone concentrations."[2]
17	A. Elisabeth Hak, *Low Levels of Endogenous Androgens Increase the Risk of Atherosclerosis in Elderly Men: The Rotterdam Study*, 87 J. CLIN. ENDOCRINOL. & METAB. 3632	"We found an independent, inverse association between levels of endogenous testosterone and severe aortic atherosclerosis and progression of aortic atherosclerosis in men."

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[2] Metabolic syndrome is a set of "risk factors" that places a person at a "higher risk" of cardiovascular disease. AM. HEART ASSOC., *About Metabolic Syndrome*, http://www.heart.org/HEARTORG/Conditions/More/MetabolicSyndrome/About-Metabolic-Syndrome_UCM_301920_Article.jsp

	(2002)	
18	Molly M. Shores et al., *Low Serum Testosterone and Mortality in Male Veterans*, 166 ARCH. INTERN. MED. 1660 (2006)	"In an unadjusted model, low testosterone levels were associated with an increased mortality risk of 88% greater than that for men with normal testosterone levels. In the fully adjusted model, which included the covariates of age, medical morbidity, BMI [body mass index], race and other clinical factors, low testosterone level continued to be associated with an increased mortality risk of 88% greater than in men with normal testosterone levels."
19	G. Corona et al., *Diagnosis and treatment of late-onset hypogonadism: Systematic review of meta-analysis of TRT outcomes*, 27 BEST PRACTICES & RES. CLIN. ENDOCRINOL. & METAB. 557 (2013)	The researchers concluded that "severe hypogonadism" was "predictive" for cardiovascular mortality.
20	Gerald B. Phillips et al., *Are Major Risk Factors for Myocardial Infarction the Major Predictors of Degree of Coronary Artery Disease in Men?*, 53 METAB. 324 (2004)	"On the basis of this and our previous study [Phillips et al. study discussed above], 3 factors are proposed that could be determinants of degree of CAD [coronary artery disease] and could link risk factors for MI [myocardial infarction] to CAD; they are age, HDL-C [high-density lipoprotein-cholesterol], and FT [free testosterone]. Each of these factors was independently associated with degree of CAD . . . and there is evidence linking each of them to major risk factors for MI."
22	GMC Rosano et al., *Low testosterone levels are associated with coronary artery disease in male patients with angina*, 19 INTERN. J. IMPOTENCE RES. 176 (2007)	"In conclusion, our data confirm that a significant relationship exists between testosterone plasma level and the severity of coronary atherosclerosis, suggesting that low testosterone may be one of the causes rather than the consequence of cardiovascular disease in men. These data complement those reported in larger studies and suggest the importance to evaluate the androgen status in patient with CAD [coronary artery disease] and the eventual need of androgen replacement therapy."
22	Peter J. Pugh et al., *Bio-Available Testosterone Levels Fall Acutely Following Myocardial Infarction in Men: Association with Fibrinolytic Factors*, 28 ENDOCRINE RES. 161 (2002).	"We have found that men presenting with acute myocardial infarction have lower levels of bio-available testosterone . . . than control subjects. Indeed, 15 out of 22 patients (68%), bio-available testosterone levels were below the normal range . . . . Lower baseline testosterone levels were associated with complications following myocardial infarction. These findings are in keeping with previous data suggesting . . . an association of low testosterone levels with risk factors for acute myocardial infarction."

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| 23 | Mohamad J. Mohamad et al., *Serum levels of sex hormones in men with acute myocardial infarction*, 28 NEURO. ENDOCRINOL. LETT. 182 (2007) | "TT [total testosterone] [and] FT [free testosterone] were significantly lower in AMI [acute myocardial infarction] patients than in patients with OMI [previously suffered myocardial infarction] and NC [normal coronary arteries]." (Citation omitted). |